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W. J. R. Heinekamp

Effect of Adrenalin on the heart



EFFECT OF ADRENALIN ON THE HEART WITH  
SPECIAL REFERENCE TO THE SLOWING  
WITH VARIATIONS IN PRESSURE

BY

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THESIS

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY  
SUPERVISION BY WALTER JOHN RICHARD HEINEKAMP  
ENTITLED EFFECT OF ADRENALIN ON THE HEART WITH SPECIAL  
REFERENCE TO THE SLOWING WITH VARIATIONS IN PRESSURE  
BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR  
THE DEGREE OF MASTER OF SCIENCE IN PHARMACOLOGY

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I

ADRENALINE, THE BASE.



In 1849 Thomas Addison (17) "as a first and feeble step toward inquiry into the functions and influences of these (suprarenal capsules) organs as suggested by pathology" put forth his paper "On the constitutional and Local Effects of Disease of the Suprarenal Capsule" in which he describes a fatal entity characterized clinically by "anemia, general languor and debility, remarkable feebleness of the heart action, and a peculiar change of color in the skin." A greatly reduced blood pressure accompanies this condition. (11)

It was not until 1856, however, that Vulpian (91) observed that the medulla of the glands contained a substance which when expressed and treated with iodine produced a rose tint which persisted for a long time, and a glaucous color with salts of iron. His observations were confirmed by Virchow (89), Arnold (12), Krunkenberg (51) and Brunner (23) none of whom was able to isolate the chromogen. Vulpian (92) working with Cloez failed, too, in the finding of the chromogenic substance.

Stimulated by the discovery of the blood pressure raising substance in the adrenal glands by Oliver and Schäfer (71-72) in 1895, and independently a year later by Scymonowicz (79) and Cybulski (28), who followed the latter, many investigators undertook the problem of isolation of the pressor substance.

Moore (69) found that a glycerine or water extract of the gland contained the active principle. He was unable to isolate any crystalline substance, and concluded that Vulpian's chromogen and the pressor substance were identical, and that the intensity of the color produced by iodine was proportional to the amount of the substance present. Abel and Crawford (5) were able to





completely precipitate the pressor constituent from an aqueous extract of the gland with benzoyl chloride and sodium hydroxide.

A year later, 1898, Abel (1) announced that he had been able to isolate the active principle of the suprarenal capsule in the form of a light gray to brownish powder to which he assigned the formula  $C_{17}H_{15}NO_3$ . He found, however, that small quantities of the new base did not effect the blood pressure being inactive in this respect. He later found his first formula too large and reduced it to  $C_{10}H_{11}NO_3$  (Abel 2-3-4).

Von Fürth (90) was able to form a relatively pure substance by precipitating the active principle as an iron compound. He did not produce a pure entity, for he found that his compound had a varying composition. Von Fürth termed this impure but highly active preparation "suprarenin." He concluded that "Abel's epinephrin and the pyrocatechin like substance, suprarenin, are thoroughly different substances and that the pressure raising action is specific to the suprarenin only." Abel contended it was due to the different methods of preparation that the products varied.

Takamine (86-87) believed that neither Abel nor Von Fürth had produced a pure substance, and in 1901 announced that he had been able to separate a light white micro-crystalline substance from the medulla of the gland. It crystallized in five forms (1) prisms, (2) rhomboid plates, (3) fine needles, (4) boat or leaf shape, (5) wart like. Takamine with a fraction of a drop of a 1-50,000 solution of his compound was able to completely blanch the conjunctiva.

Aldrich (8-9) in the same year produced a crystalline





substance which on analysis he stated to be identical with that precipitated by Takamine. Aldrich assigned the formula  $C_9H_{13}O_3N$  to the product, and this empirical formula is now assumed as correct.

Abel (4) in 1903 by what he termed his "trichloroacetic acid method" obtained a white crystalline product which was contaminated with mineral constituents to the extent of 10 to 12 percent. He considered that neither Takamine nor Aldrich had produced a pure product.

In 1911 Abel and Macht (6) isolated and demonstrated the action of a compound from the parotoid gland of *Bufo agua* which they assumed to identical with epinephrin. Biedl and Weisel (17) have shown that extracts of the retro-peritoneal chromaffin tissue in man have the same effect on the arterial pressure as have extracts of the adrenal gland. Fulk and Macleod (37) following this work but using more refined methods were able to show that acid extracts of chromophil tissue of man, dog, cat, rabbit, guinea pig, white rat, calf, sheep, and pig have the same physiologic action on the intestine and uterus muscle as has the active principle of the medulla of the suprarenal gland. Crawford and Wanatabe (24) believe that the pituitary extracts contain adrenalin or a very similar compound.

The synthesis of adrenalin was quickly accomplished after the crystallization of the extract. Stoltz (85) in 1904 obtained a product physiologically similar to adrenalin but not crystalline. Davin (29) and Flächer (35) followed with similar products, the latter producing an optically active substance identical with adrenalin.



II  
PREVIOUS INVESTIGATIONS  
OF THE  
PHYSIOLOGICAL ACTION  
OF  
ADRENALIN



Brown-Sequard (22) following the work of Addison investigated in various animals the effect of the removal of the suprarenal capsule and concluded that:-

1. The suprarenal capsules are essential to life.
2. Suppression of their secretion is more rapidly fatal than suppression of urine.
3. The function of the capsules was to destroy a substance which had the property of transforming itself into a pigment.
4. In an animal from whom the glands were removed the blood became poisonous and when injected into another animal of the same species often proved fatal.

Following these conclusions a host of investigators took up the problem some confirming and some taking issue with Brown-Sequard's results. The majority of this group of investigators contented themselves with watching the results of total and partial extirpation of the glands.

Pellacani (73) alone and ten years later in conjunction with Foa (36) investigated the effect of injecting extracts of adrenal glands into animals. They found "that altho after subcutaneous injection the animal appeared for a time to be unaffected it was invariably found dead the next morning". The adrenal glands of dogs and calves were used for injection, and rabbits, dogs, and guinea pigs as experimental animals. They were more concerned with the toxicity of the gland extracts and did not study the physiological effects of injections.

Issue was taken with these observations of Pellacani and Foa by Alexander, Matter, Marino-Zucco and others who in the main attributed the toxicity to the large quantities of neurine





which Marino-Zucco found in the gland.

It was not until 1895, however, that Oliver and Schäfer (71-72) investigated the actions of extracts of the gland when injected intravenously. They used watery extracts mainly, but also those made with dilute alcohol, and with glycerine, using approximately one part of capsule to six parts of water. In later experiments they used dried gland of calf, sheep, guinea-pig, dog, and man, in a ratio of one to eighteen and even one to one-hundred and found the physiological effect to be the same in all cases. Chloroform and morphine occasionally with atropine were used for anaesthesia. The material was injected intravenously. They also perfused the arterial system after destroying the brain and cord.

Their results may be tabulated:-

1. Extreme contraction of the arteries of peripheral origin.
2. A remarkable and rapid rise of blood pressure which took place in spite of powerful cardiac inhibition, and which became further augmented when the vagi were cut.
3. Central vagus stimulation so pronounced that the auricles stopped for a time, while the ventricles contracted with slow independent rhythm.
4. Great acceleration and augmentation of the contraction of the auricles and ventricles after section of the vagi.
5. Respiration only slightly affected.

I need not include here the results they obtained from muscle, gland, etc. for I am most concerned with the vascular system.

Scymonowicz (79) a year later independently reached





similar conclusions to those of Oliver and Schäfer. He differs in a few minor principles especially in stating that the extract instead of acting peripherally, stimulates the vaso-constrictor center.

Cybulski (28) obtained the same results as Scymonowicz, but he found that the pressor substance was in the blood taken from the suprarenal vein, and that injection of this blood into an animal produced physiological results.

Since these investigators announced these findings a host of workers have taken up the problem and have but little altered the original statements. Biedl was one of the first to confirm Oliver and Schäfer. He was followed by Velick, Gottlieb, Frankel and Acañia all of whom in general substantiated the original investigations.



III  
THE SITE OF ACTION  
OF  
ADRENALIN



Oliver and Schäfer in their original communication state that while the adrenal extract stimulated the vagus inhibitory center directly, it acted peripherally on the blood vessels causing vasoconstriction. They were of the opinion that this action was directly on the muscle. Lewandowsky (60) in 1898 noted that adrenalin when injected intravenously produced the same effects on the smooth muscle of the eye and orbit as does stimulation of the sympathetic nerves, i.e. widening of the pupil, retraction of the nictitating membrane, protrusion of the bulb, and opening of the eye-lid. He assumed that it was, a peripheral action, but found that local application was without effect.

In a later communication (61) he stated that the seat of action was in the muscle substance for it occurred after section of the cervical sympathetic or extirpation of the superior cervical ganglion with subsequent degeneration of the peripheral fibers. Boruttau (18) held the opinion that the action was in the muscle substance since it persisted after curare.

Langley (53) showed that adrenal extract had an inhibiting action on the intestinal sphincters and increased the flow of saliva. Later (54) he concluded that the extract caused a brief but active secretion of the salivary glands which is unaffected by degeneration of the sympathetic nerves. He also found that it acted after atropine had paralyzed the chorda tympani nerve. He stated the effects produced by suprarenal extract are almost all such as are produced by stimulation of some one or other of the sympathetic nerves. He believed, nevertheless, that the extract acted directly on the unstriated muscle of the hair, eye, and blood vessels and that probably in all cases the action was direct.





His conclusions were provisional.

Kuliabko and Alexandrowitsch (52) thought that since adrenal extract produced a spasm of the vessel walls by direct action on the muscle, it should by analogy strengthen the tonus and perhaps effect "pendulum contractions" in the intestines. In fact, however, they found that the extract effected great relaxation of the bowels and inhibited the contractions. They make notice of the fact that Bottazzi obtained similar results in his experiments on the oesophageal muscle of *Bufo vulgaris*.

Dixon (30) concluded that, since after large doses of apocodeine which paralyzed the vasomotor endings, adrenalin had no effect, its action must be on these terminals. Scott-Macfie (78) found that extracts of the suprarenal glands were without effect on the embryonic heart. Since Pickering (74) states that the heart, of the chick embryo of 60-75 hours is without nervous elements, one might infer from Macfie's results that the action is on the nerve endings. Brodie and Dixon (19) determined the absence of vasomotor nerve supply in the pulmonary arterioles. They also found that adrenalin when perfused through the lung does not affect the rate of flow of arterial blood.

Meltzer and Auer (67) concluded that section of the cervical sympathetic markedly influenced the action of adrenalin on the vessels in the rabbits ear. They found that after injection the maximum contraction was reached in a few seconds and after persisting five or six minutes vanished, while on the side with the nerve cut, constriction appeared later and after being effective for an hour or so gradually gave way to dilatation. Also that injection or instillation into the conjunctival sac was without





avail as was subcutaneous injection, but that after removal of the superior cervical ganglion, instillation and subcutaneous injection affected marked dilatation.

Elliott (32) after thorough study of the problem stated "Its single characteristic is the aptness to stimulate plain muscle and gland cells that are or have been in functional union with sympathetic nerve fibers". He concluded:-

1. "The reaction of plain muscle to adrenalin is of similar character to that following excitation of the sympathetic visceral nerves supplying that muscle. In default of sympathetic innervation plain muscle is indifferent to adrenalin."

2. "A positive reaction to adrenalin is ample proof of the existence and nature of sympathetic nerves."

3. "Plain muscle which has been denervated shows an increase of capacity for irritation."

4. "Stimulation takes place at the junction of the muscle and nerve."

5. "The irritable substance at the myoneural junction depends for continuance of life on the nucleoplasm of the muscle cell, not the nerve cell."

Langley (55) in a later paper compromises the statements (1) that adrenalin acts on the sympathetic nerve endings and (2) that it acts directly on muscle by stating that there is a material in cells under control of the sympathetic system, and that material is especially excited by adrenaline. It is probable that this theory had its origin with Schäfer (76). It appears that the difference in theories of Elliott and Langley are merely verbal. While these views are most plausible, neither are universally accepted.



Barger and Dale (14) have found a number of amines which produce similar results to adrenalin to which they have applied the term "sympathomemetic amines". They do not believe as inferred from Elliott and later extended by Dixon and Hamell (31) that stimulation of the sympathetic endings produces a hormone, adrenin, at the terminals which in turn produces the physiologic results. Hoskins and Lovelette (45) state that the general supposition is that in the normal animal adrenalin causes a slowing of the heart, the depression being a reflex effect resulting from the high blood pressure. Gasser and Meek (39) conclude that intravenous injection of epinephrin under conditions closely simulating adrenalin discharge causes not only increased blood pressure but generally also accelerated pulse. Hoskins and McPeck (46) found that there was depression with the discharge of small amounts of adrenalin, but with vigorous massage of the gland a rise in pressure resulted.

The more modern literature throws no additional light on the question but merely adds to the confusion. It may be briefly stated that at present adrenalin may be said to stimulate the sympathetic ending whether it be Elliott's "myoneural junction" or Langley's "receptive substance." The fact is, however, that adrenalin and stimulation of the sympathetic nerves produce almost identical results in all cases. For table of comparisons see Langley (53) and Biedl (88).

The influence of adrenalin on the central nervous system is a much mooted question. Oliver and Schäfer (71) were of the opinion that the extract stimulated directly the vasoconstrictor center. Brown (21), Biedl and Reiner (16), Cybulski (28) found





evidences of action directly on the cardio-inhibitory center.

Nice, Rock and Courtwright (70) among others mention respiratory acceleration after adrenalin and believe it to be due to central action. The questions of central action will be discussed further in the body of the thesis.



IV  
THE ACTION OF ADRENALIN  
ON THE  
TURTLE HEART





Oliver and Schäfer in their original communication stated that the inhibition of the heart following the injection of adrenalin was due to stimulation of the cardio-inhibitory center. Since that time Brown (21), Biedl and Reiner (16), Cybulski (28) and others have shown that adrenalin extract or solution of the desiccated gland, when injected into the cephalic end of the carotid artery of dogs, produces a distinct slowing of the heart previous to the rise in pressure. Many other experimenters (Brown, Nice, Rock and Courtwright (70) mention the respiratory acceleration after adrenalin, and seem to think it due to direct central action. As a result of our work with turtles we have come to a similar conclusion, that adrenalin, at least in this animal exerts a direct action on the vagus centers.

In this investigation it was our object to obtain evidence of the direct action of adrenalin on the medullary centers. To do this we resorted to brain perfusion as the most simple and reliable method. We prepared our turtles by cutting the cord low enough to preserve the medulla, and usually between the third and fourth cervical vertebrae. In order to reduce the number of spontaneous movements to a minimum, the cord was pithed. Later we found it advisable to break the femurs and humeri and cut the abdominal muscles in order to abolish all movements.

The two carotid sheaths and their contents were carefully dissected out as high up in the neck as possible in order that the drug may more quickly reach the medulla, and also that less resistance would be offered by any vaso-constriction. The vagi nerves were isolated and subjected to stimulation in order to determine their effectiveness in producing inhibition. We found the right



considerably more effective and sensitive than the left vagus.

It was not thought necessary to tie off all the heart vessels so long as none of the drug was allowed to enter the general circulation and hence exert a direct action on the heart. It is evident that the heart, when all the large vessels are tied off, as is usually done in perfusing the brain, may develop an abnormal beat and hence would not in all probability respond in a normal manner to central stimulation. We were concerned, therefore, with retaining as near a normal beat as possible. To effect this a ligature was passed around the neck, excluding the two carotid sheaths and their contents, and tightly drawn between the third and fourth cervical vertebrae. Opening a few veins amply takes care of the excess fluid. In this manner the head is practically isolated from the body, but the heart is still under the influence of the vagus centers through the vagi nerves.

A cannula was inserted into the right carotid and in our first experiments the left was tied off; but in our later ones, to exclude the probable effect of anemia at least in a large degree, the left was not occluded. The solutions used - 1:50,000 adrenalin, 1-10,000 strychnine sulphate, and 0.9 per cent salt solution and 1:100,000 - adrenalin were run in from bottles under such a pressure that perfusion was possible, but that the liquid did not back up into the left carotid and hence act directly on the heart.

In a few cases adrenalin was injected directly into the heart muscle with the same results as obtained by many investigators: namely, that the amplitude and rate are increased, adrenalin acting as a stimulant.





## EXPERIMENT I

The normal heart rate for this animal, under the conditions of this experiment, was 29 per minute and after perfusion with salt solution it increased to 31. A 1-50,000 adrenalin solution was next used and in three minutes and ten seconds the heart was totally and abruptly inhibited. There was no gradual slowing for just previous to the inhibition the water was 31. Normal salt solution was then used and in a somewhat general manner the heart rate returned to 33. It took about two minutes after the salt perfusion for the heart to return to normal.

A 1-10,000 strychnine sulphate solution was next used with the idea that it might sensitize the cells of the vagus centers that they be more easily influenced by adrenalin and hence produce aggravated results. Partial inhibition was effected by the strychnine, the heart rate dropping to 4. Just preceding this slowing the rate increased to 39. A 1-50,000 adrenalin solution was next run in and in five minutes complete inhibition was again effected. It seems rather improbable that strychnine sensitized the nerve cells in this animal, but probably stimulated them to some extent.

With a return to salt solution the heart rate increased to 38, but gradually fell to normal, 31. A 1-100,000 solution of adrenalin was used and partial inhibition was effected, the rate dropping to 12 in one minute. However, there was a gradual return to normal due in all probability to a stoppage in the circulation of the fluid.

We have found it impossible to effect these results for any length of time after perfusion has been started. There are three





possible causes for this; (1) anemia; (2) tolerance being established; (3) fatigue of the center. It is well known that nerve cells suffer readily from lack of nutrition, and, since in this experiment no nourishment was being brought to the centers, one is justified in assuming that the nerve cells failed to react to the adrenalin stimulation because of the deprivation of metabolic material. It is possible that tolerance was established for it has been found that continued use of some drugs produces a tolerance for those drugs. Although we have no definite means as yet for differentiating between the tolerance and fatigue in the turtle under the conditions of this experiment we feel justified in saying that tolerance may be a factor worthy of consideration. Fatigue of the center is the third probability, but due to an absolute anemia being produced it is quite impossible to determine whether fatigue is a factor under the present conditions. We, ourselves, feel that the anemia is responsible for the greater part, but do not cast aside fatigue and tolerance as unimportant. (See Table I)

## EXPERIMENT II

In experiment I, distilled water was used as a solvent. It may be assumed that this fluid, by producing osmotic changes and anemia might exert some influence on the heart rate. In order to disprove this we perfused the brain of this turtle with distilled water. Inhibition was not produced, but following this procedure adrenalin inhibition could not be effected due in all probability to the production of absolute anemia by the distilled water. A 1:1,000 adrenalin solution (1 cc.) was injected directly into the heart muscle. The amplitude of this beat was increased



enormously, 75 to 100 per cent. Acceleration was also effected. Since the sympathetics to the heart in this animal are less functionally developed than in mammals, we should not expect any increase in rate from stimulation of the myoneural junctions. We base this statement on the fact that the vagus is not well developed in the turtle as in mammals, for a stronger stimulus is necessary to elicit inhibition of the turtle heart than of the dog heart, and also because the left vagus is in a majority of the cases irresponsive to stimulation; and hence there is no reason to assume that the sympathetic system, which is of later development and which requires even a stronger stimulus than does the vagus to produce proportional results, is as well developed functionally as the vagus. We may conclude from this indirect evidence that adrenalin exerts a direct influence on the heart muscle.

### EXPERIMENT III

The routine of this experiment was the same as in the above two with the exception that 0.9 per cent salt solution was used as a solvent. The left carotid artery was left open so that the brain received a partial supply of blood at least. The pressure of the inflow was such that perfusion was possible but still not great enough to force the liquids back down the open left carotid artery.

The normal rate was 38. Adrenalin 1-50,000 produced total inhibition in one-half minute. With salt solution alone the heart rate became 43, but with the return of adrenalin total inhibition resulted in one minute. Perfusion with salt solution caused the heart to beat at 40.

The promptness with which the centers responded to adrena-





lin solution in this experiment, we thin' is due at least in a degree to the better nutrition of the cells. Strychnine was not used because of its central inhibiting action.

(See Table 2)

#### EXPERIMENT IV

The technique of this experiment was the same as that of three. The normal heart rate was 40. After perfusion with salt solution for about five minutes the rate was 43. 1-50,000 adrenalin was then used, total inhibition resulting in 4 minutes. With return of salt solution the heart rate became 38.

(See Table 3)

#### EXPERIMENT V

The normal rate of this turtle heart was comparatively slow, normal being 19. Perfusion with salt solution effected no changes. After adrenalin, however, the rate dropped quickly to 6; and with the return of salt solution a normal rate was assumed. Adrenalin perfused through the cerebral vessels a second time slowed the heart to 5. Salt solution again effected a normal rate, and adrenalin the third time slowed the heart to 8. Complete inhibition was not effected. An extremely strong current applied to the right vagus was necessary to slow the heart. The left vagus did not respond to stimulation. Anemia or tolerance was produced for perfusion a fourth time with adrenalin elicited no changes at all.

(See Table 4)

In all we used nine turtles with identical results except in turtle II when an absolute anemia probably resulted from the perfusion with distilled water.





## CONCLUSIONS

From these experiments we may conclude that:-

1. Adrenalin exerts a direct action on the cardio inhibitory center of the turtle stimulating it and hence producing stoppage of the heart.

2. Due to central anemia, fatigue, or tolerance being established adrenalin exerts no action after repeated use.

3. Adrenalin when injected directly into the heart muscle acts as a stimulant, increasing both rate and amplitude, systole being most affected.

4. Strychnine exerts some action on the medulla which produces partial inhibition.

5. Adrenalin is not any more efficacious after strychnine than before.



TABLE I

Heart Rate	Remarks
29	Normal
31	After salt perfusion
Inhibition	After 1-50,000 adrenalin sol.
33	After salt perfusion
4-9	After strychnine 1-10,000
39	After salt solution
Inhibition	After 1-50,000 adrenalin
38-31	After salt solution
12	After 1-100,000 adrenalin
37	After salt solution



TABLE 2

Heart Rate	Remarks
38	Normal
Inhibition	After 1-50,000 adrenalin
43	After Salt solution
Inhibition	After 1-50,000 adrenalin
40	After salt solution

TABLE 1	
SUMMARY OF RESULTS	
PERIOD OF 1910-1911	
1. The first year of the war was a year of great suffering and distress for the people of the United States.	2. The second year of the war was a year of great suffering and distress for the people of the United States.
3. The third year of the war was a year of great suffering and distress for the people of the United States.	4. The fourth year of the war was a year of great suffering and distress for the people of the United States.
5. The fifth year of the war was a year of great suffering and distress for the people of the United States.	6. The sixth year of the war was a year of great suffering and distress for the people of the United States.
7. The seventh year of the war was a year of great suffering and distress for the people of the United States.	8. The eighth year of the war was a year of great suffering and distress for the people of the United States.
9. The ninth year of the war was a year of great suffering and distress for the people of the United States.	10. The tenth year of the war was a year of great suffering and distress for the people of the United States.



TABLE 3

Heart Rate	Remarks
40	Normal
43	After salt solution
Inhibition	After 1-50,000 adrenalin
38	After salt



TABLE 4

Heart Rate	Remarks
19	Normal
19	After salt solution
6	After adrenalin
18	After salt solution
5	After adrenalin
18	After salt solution
8	After adrenalin

TABLE I	
Year	Amount
1890	100
1891	100
1892	100
1893	100
1894	100
1895	100
1896	100
1897	100
1898	100
1899	100
1900	100
1901	100
1902	100
1903	100
1904	100
1905	100
1906	100
1907	100
1908	100
1909	100
1910	100
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2063	100
2064	100
2065	100
2066	100
2067	100
2068	100
2069	100
2070	100
2071	100
2072	100
2073	100
2074	100
2075	100
2076	100
2077	100
2078	100
2079	100
2080	100
2081	100
2082	100
2083	100
2084	100
2085	100
2086	100
2087	100
2088	100
2089	100
2090	100
2091	100
2092	100
2093	100
2094	100
2095	100
2096	100
2097	100
2098	100
2099	100
2100	100

V  
THE MODIFICATION  
OF THE  
ACTION OF ADRENALIN  
BY  
MORPHIN





Oliver, Schäfer(71) and others, while investigating the action of adrenalin used morphin with ether or chloroform as an anesthetic. According to Brown (21), Cybulski (28) and as I have recently found in my work on turtles (43) a direct action on the medullary centers while morphin in the dog produces a slow irregular pulse from powerful stimulation of the vagus centers (Cushny (25)). Many investigators who use morphin-ether anesthesia are able to elicit marked inhibition of the heart, following an injection of adrenalin. This inhibition has been attributed to stimulation of the cardio-inhibitory center by the rise in blood-pressure (26).

While studying the action of adrenalin on the dog's heart, it occurred to me that morphin by its central action might influence the effect of adrenalin. In the experiments recorded below, especial attention has been given to the modification of the adrenalin action by this alkaloid.

The animals were prepared in the usual manner for recording carotid pressure. The drugs were given by intravenous injection into the femoral vein and were washed in with 5 cc. of normal salt solution from a burette. After normal tracings were recorded, adrenalin in varying amounts was injected; and when the blood pressure had returned to normal 0.008gram of morphin sulphate was given intravenously. The results of a subsequent dose of adrenalin were then compared with those produced previously to the morphin. The blood pressure in some of the experiments was raised artificially either by stimulation of the splanchnic nerve, or preferably by occluding the abdominal aorta. After this the vagi were generally cut, and adrenalin again injected. The res-



piration was not always recorded, but when recorded mention is made of it.

In a series of seventeen dogs inhibition was produced in fourteen or eighty-two per cent. In two young animals and one old pregnant bitch slowing was not elicited by any amount of adrenalin either before or after morphin. It is probable that the vagus mechanism is not as sensitive or as well developed in the young dog as in the old. I found five dogs in this series in which inhibition was not produced previous to but did occur after morphin.

Although unable to make such statements as have Meek and Eyster (64) who state that intravenous injections of physiological amounts of adrenalin in dogs with good vagal tone invariably causes a decrease in heart rate, or to conclude as does Hoskins and Lovelette (45), who used dogs with rapid pulse and high blood pressure, that adrenalin produces not only an increase in blood pressure but generally also an accelerated pulse, I have found that as a rule dogs with high blood pressure and quickened pulse (conditions which indicate poor vagal tone) adrenalin alone produces acceleration only, and inhibition only after morphin had been given.

Stewart and Rogoff (83) in a recent article state the concentration of adrenalin in the serum which they think is very nearly the possible normal maximum to be 1:560,000. I have found this physiological dose quite ineffective. In fact in only one dog under chloroform anesthesia was inhibition elicited with 1 cc. of 1-100,000 adrenalin in any of our experiments. I shall report the effect of chloroform on adrenalin action in a subse-





quent paper. In the present work we used large doses, but generally employed a 1-10,000 solution in amounts within therapeutic limits; while doses of 1 cc. of 1-2,000 adrenalin have been injected without any inhibition being produced.

Stewart and Rogoff (84) have found that a fresh solution of adrenalin hydrochloride yielded on colorimetric examination 56 to 80 per cent of base. I am of the opinion that the powder is a more stable product, but I have found that rapid oxidation takes place even in dark stoppered bottles. I used the tablet adrenalin of Parke, Davis and Company, Fresh solutions being prepared before injection.

#### EXPERIMENT I.

This experiment is one of a series of eleven which agree in all but a few minor details. They were performed in order to determine the influence of morphin on adrenalin action.

The normal pulse was 171; systolic pressure 126 m.m. Hg. and respiration 108. Following the injection of 1 cc. of 1-10,000 adrenalin the pressure to 183 m.m. Hg. and the heart rate became 189 an acceleration of 10.6 per cent. An injection of 1 cc. of 1-2,000 adrenalin increased the pressure 72.7 per cent and the pulse 27 per cent. 0.016 gram of morphin given intravenously did not affect the heart rate although the respiration slowed a little. 1 cc. of 1-10,000 adrenalin produced a rise of 57.6 per cent and an acceleration of 2 per cent. It is probable that no sufficient time was given for the morphin to exert its action for subsequent doses of adrenalin produced inhibition. 1 cc. of 1-2,000 adrenalin slowed the heart 36 per cent while increasing the pressure 82.2 per cent. 1 cc. of 1-10,000 adrenalin effected 9 per cent inhibition with an exceptionally characteristic and very marked





rise of 54 per cent. After physostigmin the heart accelerated 6.5 per cent. 1 cc. of 1-2,000 adrenalin now produced a slowing of 57 per cent with a rise of 50 per cent. From this experiment it is quite evident that the slowing is in proportion to the dose and not the rise in pressure. The marked results after physostigmin are probably due to the sensitizing effect of the drug on the vagus endings. This action of adrenalin is central for after section of the vagi inhibition is not effected. The entire experiment is given in table V.

#### EXPERIMENT II.

A series of four experiment all of which agreed in essentials and of which this one is typical were performed to determine (1) whether morphin sensitized the vagus center, and (2) whether the slowing produced by adrenalin after morphin was greater than that produced by artificially raising the pressure.

A male dog weighing about 8 kilograms and fairly well nourished was used. The normal pressure was 130 mm. Hg. and the pulse rate was 168. 1 cc. of 1-10,000 adrenalin produced a rise in pressure followed by a fall during which the pressure became sub-normal. During the fall the pulse increased to 210. Pressure was increased by partially occluding the abdominal aorta, for stimulation of the splanchnics did not produce the required rise. The pressure was increased from 96 mm. Hg. to 160 mm. Hg. No slowing occurred. 0.008 gram of morphin sulphate was injected. The pressure was again mechanically increased from 46 mm. Hg. to 116 mm. Hg. There now occurred distinct evidence of vagus inhibition the pulse slowing from 192 to 150. 1 cc. of 1-10,000 adrenalin produced a rise in pressure from 64 mm. Hg. to 104 mm. Hg and then dropped to 94 mm.



Distinct partial inhibition was effected, the pulse dropping from 222 to 84. Pressure was again increased artificially from 44 mm. Hg. to 114 mm. Hg. Again evidence of vagus stimulation was effected, the heart slowing from 216 to 162. It should be noted in this experiment that while occlusion of the aorta increased the pressure 159 per cent, the inhibition was only 25 per cent, and that adrenalin causing a rise in pressure of 62.3 per cent produced a slowing of 62.1 per cent.

The experiment included below in table VII is one of two experiments agreeing in detail performed to determine (1) whether asphyxia effects inhibition of the heart and (2) whether morphin has any influence on this acceleration. It will be noticed that after the morphin asphyxia preoduced acceleration while previous to it inhibition was effected. The inhibition is in proportion to the dose of adrenalin rather than to the rise in pressure. Previous to the morphin 1 cc. of 1-20,000 adrenalin produced an inhibition of 6.4 per cent while after if slowing was 46 per cent. The asphyxia lasted about four minutes.

#### DISCUSSION.

It is the common opinion that inhibition of the heart following adrenalin is due "to the high blood pressure which induces congestion of the brain and arouses the vagus center to activity" (26). After section of the vagi this inhibition is not observed. Morphin exerts a central stimulating action on the vagus center producing a slow irregular pilse. In small amounts as I have used there is generally no decided action on the vagus center although the respiratory center is readily influenced. Adrenalin, as I have found (Section IV) and as other investigators have concluded







has a direct action on the medulla. The increased inhibition produced by adrenalin following the use of morphin may be due to either of two factors, sensitization of the medullary center by the morphin or (2) synergistic or additive action of adrenalin and morphin.

Jackson and Ewing (49) found that morphin increases the reflex excitability of the vagus centers. Morphin also excites the cord (63) while cerebral depression is primary (80). In my work the amount of morphin given was just enough to slightly depress the respiratory center. It is probable that if morphin did exert a sensitizing effect, under the condition of my experiments the action would be manifested. Using a different method than did Jackson and Ewing to determine the increased reflex excitability of the vagus center, I have found (Experiment II) that morphin, while slightly depressing the respiratory center which seems to be more sensitive to morphin than the other medullary centers, sensitizes the vagus centers. Occlusion of the abdominal aorta above the mesenteric branches, and stimulation of the splanchnics simulate the stimulation of the sympathetic myoneural junctions in the splanchnic area by adrenalin and hence we may look for similar results to be produced by adrenalin and occlusion of the aorta. But the facts are as shown by these experiments, the inhibition produced by adrenalin is greater than that produced by increasing the pressure artificially and that the inhibition effected by artificially raising the pressure is greater after morphin than previous to it. It is evident then that morphin does increase the excitability of the vagus centers as Jackson and Ewing found.

It may seem probable that since the respiratory and car-



dio-inhibitory centers are in proximity that they should be acted upon similarly by the same drug. But the fact is that morphin while depressing the respiratory center actually sensitizes and stimulates the vagus center. That this albaloid acts differently upon these medullary centers is no more startling than the fact that atropine selectively acts upon the autonomic endings, and not on the sympathetics; or that morphine while chiefly depressant in the dog induces wild excitement in the cat; or that aconite affects only the sensory nerve endings; or that curare acts on the nerve endings of striated muscle. The results of my experiments I think show a difference in action of morphin on the medullary centers.

Since morphin sensitizes the centers one might suppose that they would respond more quickly and strongly to a rise in blood pressure and hence produce an aggravated slowing. However, I think that Experiment II amply proves that it is not the rise in pressure that is the cause of the slowing. In one experiment adrenalin produced a greater slowing, 62.1 per cent, after a smaller rise in pressure 62.3 per cent, than was effected by a greater mechanical rise of 159 per cent. I have found in certain experiments that 1 cc. of 1-10,000 adrenalin might produce a greater rise in pressure than 1 cc. of 1-2,000 adrenalin, but that the latter dose produced very marked slowing where as only acceleration was produced by the former. I have also found that the inhibition is in relation to the size of the dose rather than in relation to the rise in pressure as I would expect were the latter the causative agent.

The second possible cause for this aggravated adrenalin action following the use of morphin is either an adrenalin-morphin additive or synergistic reaction. I feel that it is not an addi-





tive action from the fact that the quantities of morphin I used were not sufficient to produce any signs of vagus inhibition. Therefore I am inclined to beleive that adrenalin and morphin have a synergistic action.

The rise in blood pressure plays probably but little part in the slowing of the heart rate for the following reasons; (1) The degree of inhibition is not proportional to the rise in pressure as I should expect, but it is in direct proportion to the size of the dose. (2) The centers being very delicate in reaction if stimulated by the high pressure would not continue to respond when the pressure had returned to normal; but as I have found slowing persists after return to normal pressure. (3) It is hardly permissible to assume without more adequate basis, and from my experiments I am unable to offer any, that the cardio-inhibitory center is set to react to a definite rise in pressure and is not influenced by one lesser nor greater than this specific one. However. in none of my experiments have I found that the rise in pressure has a definite relation to the degree of slowing. (4) If blood pressure alone were the cause I would expect an equal degree of slowing previous to and after morphin to be produced by an equal rise in pressure. This is amply disproved in my experiments.

A third possibility is that adrenalin sensitizes the centers and that morphin is then able to produce inhibition by its stimulating powers. I feel that this is not the cause however, since sufficiently large doses which cause an extreme rise in pressure have been given previously to morphin without any inhibition being produced. If the increased blood pressure stimulated the vagus centers, and if adrenalin sensitized the vagus centers I





should expect slowing to occur in the cases mentioned. However, I am unable to draw any further disproof of this postulation from my experiments.

Starling (82) in writing of the cardio-inhibitory center states that " anything which interferes with the gaseous exchange of the center calls forth an increased state of activity of the center." " This is due to one of two things (1) excess of carbon dioxide or (2) lack of oxygen." However, in asphyxia the rise in blood pressure is more important in slowing the heart. Berezin(15) working with rabbits and large fish ( pike) , and Wiggers ( 93) using the brains of decapitated dogs have found that adrenalin in higher concentrations than are necessary to produce proportional peripheral results produce a constriction of the cerebral vessels.

One may postulate that adrenalin by constricting the cerebral vessels produces asphyxia of the center and hence inhibition of the heart. I have found that asphyxia produces similar results previous to and after morphin. After morphin however, a slightly more pronounced slowing occurred toward the end of asphyxia than was produced before the use of the drug. In one case an actual acceleration occurred at the end of asphyxia.

Wiggers found that adrenalin in high concentrations ( 1-500 ) was necessary to produce cerebral constriction. The solutions I have used were never greater than 1cc. of 1-2,000 and in the majority of the cases much more dilute solutions of adrenalin were used so that if constriction were produced it would be very slight. The blood carries enough surplus oxygen to compensate for the deficiency in volume that would occur with constriction.

Since the greatest action of adrenalin is on the vascular



system in the splanchnic area it is more than probable that the medulla and brain even if constriction of their vessels is effected receive a greater supply of blood after adrenalin than before it. I do not thin<sup>r</sup> any degree of asphyxia which adrenalin might produce, and I am of the opinion that it does not produce any, would compare with the absolute artificial asphyxia effected in my experiments. And since no results were effected by total asphyxia I do not thin<sup>r</sup> the possible adrenalin asphyxia could play any part; also if asphyxia were the causative agent I would expect slowing to occur in instances previous to the morphine where only acceleration was effected.

I am sure that in no case when adrenalin was administered was there an acute lac<sup>k</sup> of oxygen in the medullary centers.

That adrenalin produces no results when injected into the fourth ventricle, I thin<sup>r</sup> is due to the slow absorption from this region. It is only drugs that have a strong action on the central nervous system (strychnine) or able to destroy nervous tissue (chloroform, phenol) that produce quick results when injected into the fourth ventricle. Recently Meltzer and Auer (13) found that adrenalin injected intraspinaly into the lumbar region is comparatively slowly absorbed, and Meltzer (66) found no absorption through nerves. Scott and Halliburton (77) on the contrary state that the injection of 1 cc. of 1-10,000 adrenalin into the sub-cerebellar cistern produces a rise in pressure as quick<sup>l</sup>y as if injected intravenously. It is probable that a drug so quick<sup>l</sup>y oxidized as adrenalin has not the penetrating power to permeate directly the medullary substance.





## CONCLUSIONS

1. Adrenalin has a direct central action and is synergistic with morphin.
2. Morphin to a degree sensitizes the vagus center
3. The aggravated adrenalin action following morphin is due to the morphin sensitization and adrenalin-morphin synergism.
4. The increased blood pressure plays but little part in effecting the inhibition of the heart.





TABLE 5.

Pulse	Pressure		Rise in Pressure	Inhibition.	Resp.	Remarks.
	Systolic	Diastolic				
171	126	120	45.2		108	Normal
189	183	178		-10.6	108	After 1 cc. 1-10,000 adrenalin.
168	124	114			99	Before 1 cc. 1-2,000 adrenalin.
213	214	208	72.7	-27.0	102	After 1 cc. 1-2,000 adrenalin.
162	112	106			111	Previous to morphin.
165	176	170	57.6	-2.0	96	After 1 cc. adrenalin.
105	204	192	82.1	36.0	74	After 1 cc. 1-2,000 adrenalin.
141	100	92			72	Before 1 cc. 1-10,000 adrenalin
129	154	142	54.0	9.0	69	After 1cc. 1-10,000 adrenalin.
138	112	102			69	Before 1 cc. 1-2,000 adrenalin
90	178	164	59.0	34.8	69	After 1 cc. 1-2,000 adrenalin.
150	98	90			87	Before 1 cc. 1-10,000 adrenalin
63	120	113	50.0	57.0	Inhib	After physostigmin and after 1 cc. 1-2,000 adrenalin



TABLE 6.

Pulse	Pressure		Rise in Pressure	Inhibition	Remarks
168	130	126			Normal
210	176	166	35.4	-25.0	After 1 cc. 1-10,000 adrenalin.
180	96	92	-		Before occlusion of abdominal aorta.
180	160	157	67.0	0	After occlusion of abdominal aorta.
192	46	43			Before occlusion of abdominal aorta and after morphin.
150	116	106	152.2	21.8	After occlusion of abdominal aorta and after morphin.
222	64	60			Before 1 cc. 1-10,000 adrenalin.
84	104	100	62.3	62.1	After 1 cc. 1-10,000 adrenalin.
216	44	41			Before occlusion of abdominal aorta.
162	114	108	159.0	25.0	After occlusion of abdominal aorta.

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TABLE 7

Pulse	Pressure		Rise in Pressure	Inhibition	Resp.	Remarks
	Systolic	Diastolic				
132	110	92			54	Normal
132	110	92			--	At beginning of asphyxia.
130	90	75	-18.1	1.5	--	At end of asphyxia.
124	160	130			40	After asphyxia.
124	134	114			48	Before 1 cc. 1-20,000 adrenalin
116	150	120	10.6	6.4	52	After 1 cc. 1-20,000 adrenalin.
124	116	100				At beginning of asphyxia.
88	70	58	-39.7	29.0		At end of asphyxia.
108	119	100			48	Before 1 cc. 1-20,000 adrenalin
106	152	142	20.6	1.9	54	After 1cc. 1-20,000 adrenalin.
102	85	58			46	Before 1 cc. 1-2,000 adrenalin.
72	190	140	55.2	49.0	50	After 1 cc. 1-2000 adrenalin.
98	76	52		3.6	42	After 0.008 gram morphine.
90	104	66	36.8	8.2	Irreg	After 1 cc. 1-20,000 adrenalin.
92	90	54			40	Before 1 cc 1-20,000 adrenalin.
84	124	76	37.7	8.7	40	After 1 cc. 1-20,000 adrenalin.



TABLE 7 ( concluded )

Pulse	Pressure		Rise in Pressure	Inhibition.	Resp.	Remarks
76	134	88	48.8	17.4	32	After 3rd cc. 1-20,000 adrenalin
120	96	78				Before 1 cc. 1-20,000 adrenalin.
56	174	124	81.3	53.3	8	After 1 cc. 1-20,000 adrenalin.
82	130	80				At beginning of asphyxia.
134	102	98	-21.6	-64.6		At end of asphyxia.
69	126	120			24	Before 2 cc. 1-20,000 adrenalin.
38	150	137	19.0	45.0	24	After 2 cc. 1-20,000 adrenalin.
120	16				30	Before 0.4 cc 1-20000 adrenalin.
68	124			43.3	30	After 0.4 cc. 1-20,000 adrenalin
54	136	136	17.2	46.0	40	After 1 cc. 1-20,000 adrenalin.



VI  
THE MODIFICATION  
OF THE  
ACTION OF ADRENALIN  
BY  
CHLOROFORM





Oliver and Schafer in their original communication state that the vagus inhibition produced by adrenalin is due to stimulation of the cardio-inhibitory center. They make note of the fact that in a single experiment, intravenous injection of the extract effected fibrillar contraction of the ventricles when the height of the pressure was reached. The animal used in this case was a dog under the influence of chloroform, morphin and atropin.

Previous to this time much work had been done toward determining the action of chloroform. The first Hyderabad (47) commission obtained results which tended to prove that chloroform no matter in what manner it was administered had no toxic effect on the heart until the respiration was paralysed. The second commission (48) headed by Brunton, who previous to this time believed that chloroform had a detrimental effect on the heart, arrived at the same conclusions. Wood (94) concluded that the heart might be paralyzed by chloroform. MacWilliam's conclusions were:-

1. During chloroform anaesthesia the blood pressure is lowered and the heart action weakened.
2. Dilatation of the heart occurs to an appreciable extent.
3. Cardiac failure occurs by a more or less sudden enfeeblement and dilatation of the organ.
4. The heart muscle is depressed, the cardiac walls relaxed and the functional efficiency of the heart impaired.
5. The depressing influence is direct on the cardiac mechanism and not on the vagi.
6. Occurrence of the fibrillar contraction is not the primary mode of cardiac failure in inhalation of chloroform in the



normal animal. Hare and Thornton (42) believed that chloroform produced cardiac paralysis. Gas'ell and Shore (38) in their experiments that while the vasomotor center was excited by chloroform, the heart was depressed. Hill (44) found that chloroform produced paralytic dilation of the heart, the action being a direct one on the muscle. He stated that the vagus inhibition is of no importance in the production of cardiac syncope. Keefe (50) stated that cardiacsyncope occurred only in late anaesthesia. Brodie and Russel (20) found that chloroform applied to the laryngeal mucosa produced reflex inhibition of the heart. Rpsenfeld (75) in his experiments never noted cardiac inhibition.

Embly (33) obtained the following results from hearts isolated from the vagus, vasomotor, and respiratory influences.

1. Chloroform has an immediate and progressively paralytic effect on the heart muscle.

2. Heart muscle is very sensitive to the poisonous effects of chloroform.

3. Inhibition of the heart might be brought about by chloroform inhalation by 1- reflex excitation of the sensory terminals in the respiratory passage, 2- by increasing the vagus excitability so that the usual control exercised by the vagi is increased.

Levy (56) reported that varying percentages of chloroform produced different results. Lewis and Levy (59) continuing this work found that low tensions of chloroform vapor administered to cats produced high grades of irregularity of the heart. Levy (57) alone reported later that the "mammalian heart when under the influence of chloroform is in an irritable condition. This





irritability is raised under conditions of light anaesthesia and lowered under deep anaesthesia. He attributes death under chloroform to ventricular fibrillation which may be prevented by steadily maintaining a full degree of anaesthesia. In a later work (58) he states that dilatation of the ventricles is a condition which is protective against ventricular fibrillation. He explains the protective action of full anaesthesia on this ground. Levy worked with cats, animals which have poor vagal tone.

Embly (30) states that sudden inhibition or syncope in dogs occurs only in the period of induction of the anaesthesia, but that ventricular fibrillation may occur at any time.

Dixon states that sudden inhibition due to direct excitement of the vagal center in the medulla occurs when concentrated chloroform vapor is absorbed. He also believes that chloroform produces a rapid dilatation of the heart and a marked diminution of output, the drug acting directly on the muscle. Meyer and Gottlieb (68) state that chloroform is a powerful cardiac poison, paralysis and insufficiency resulting. Cushny (27) states that chloroform by direct action on the heart produces weakness and dilatation. The heart slows gradually and may be inhibited more easily than normally. Sollman (81) states that cardiac arrest may follow chloroform due to direct or reflex vagus stimulation or to direct paralysis of the cardiac muscle.

The influence of adrenalin has been amply discussed in the preceeding sections.

#### EXPERIMENTAL WORK.

The animals were prepared in a similar manner as that



described in section V. In some of the experiments a small this-tle tube was inserted into the pericardial cavity and fixed there by means of a purse string suture in the pericardium. By means of a tambour to which the tube was connected changes in the heart volume were easily recorded.

As in the previous experiments I used the tablet adrenalin of Parke, Davis and Company. Solutions varying in dilution from 1-1,000 to 1-100,000 were used. In this as in the previous section I shall record a single experiment typical of the series.

#### EXPERIMENT I.

A male dog weighing 6 kilograms was used. The normal pressure was 120 mm. Hg systolic and 114 mm. Hg. diastolic, and the pulse was 180. Stimulation of the right vagus totally inhibited respiration but was little effect on the heart.

One cc. of 1-100,000 adrenalin was injected intravenously, the pressure rising to 142 mm. Hg. and 136 mm. Hg. diastolic. The pulse accelerated slightly becoming 172. Respiration was unaffected.

After injecting 1 cc. of 1-10,000 adrenalin the pressure rose to 140 mm. Hg. systolic and 130 mm. Hg. distolic and then sud-dropped to 18 mm. Hg. with almost total inhibition of the heart. This was the most marked inhibition under ether anaesthesia I have seen produced by adrenalin. The heart recovered and in one minute the pressure had returned to normal. Respiration was markedly inhibited.

One cc. of 1-100,000 adrenalin increased the pressure to 140 mm. Hg systolic and 126 mm. Hg. diastolic. The pulse was 164 before and after the injection. Respiration was regular, 64. Stim-





ulation of the right vagus inhibited respiration totally and the heart slowed to 114.

One cc. of 1-10,000 adrenalin raised the pressure to 164 mm.Hg and 152 mm. Hg. It then dropped to 90 mm. Hg. systolic and 56 mm. Hg. diastolic. Respiration was unaffected. A second injection produced like results. The pressure was now raised artificially by clamping the abdominal aorta above the coeliac axis to 140 mm. Hg. without any evidence of inhibition. Respiration, however, became augmented. Repetition of this procedure effected identical results.

Chloroform was now used for anaesthesia.

One cc. of 1-100,000 adrenalin increased the pressure from 106 to 120 mm. Hg without any evidence of inhibition of the heart. One cc. of 1-10,000 adrenalin caused a rise in pressure from 110 to 120 mm. Hg. The heart slowed from 146 to 70 and the pressure dropped to 88 mm. Hg. systolic and 60 mm. Hg. diastolic. Following this stimulation of the vagus produced inhibition of the respiration and the heart rate slowed from 156 to 60. Both vagi were now cut. Injection of the adrenalin still produced marked inhibition, 1 cc. of 1-10,000 solution slowing the heart from 136 to 62. Further injection of the adrenalin tended to weaken the heart which was found greatly dilated

## EXPERIMENT II

A male dog weighing 8 kilograms was used. The normal pulse was 110, systolic pressure 126 mm. Hg. and diastolic 112 mm. Hg. Following the injection of 1 cc. 1-10,000 adrenalin, the heart rate increased to 210, and the pressure rose to 230 mm. Hg systolic





and 196 mm. Hg diastolic. There was no evidence of slowing. The heart volume was slightly changed. Respiration deepened and accelerated. After a second injection of 2 cc. of 1-10,000 adrenalin the rate increased from 126 to 162, the systolic pressure rose from 116 to 240 mm. Hg. and the diastolic from 110 to 200 mm. Hg. The heart volume was unaffected and the respiration became shallower.

Chloroform was now substituted for ether for anaesthesia. The volume of the heart almost immediately began to increase indicating that chloroform produces dilatation of the organ. An injection of 1-10,000 adrenalin increased the pressure from 138 to 208 mm. Hg., the rate changing from 100 to 120. With the rise in pressure the volume became less. However, the pressure suddenly began to fall and synchronously the volume increased. The heart action became weaker. An injection of 1 cc. of 1-10,000 adrenalin was given. The pressure rose but dilatation remained. The pressure again suddenly fell and the heart dilated further. Injection of adrenalin tended to weaken the heart, the period of primary stimulation becoming shorter. On opening the thorax the heart was found enormously dilated and fibrillating.

### EXPERIMENT III

A female dog weighing 2 kilograms was used. The normal pulse was 150, systolic pressure 94 and diastolic pressure 84 mm. Hg. One minum of chloroform was injected intravenously. Following a slight rise in pressure the heart beat became almost imperceptible and the pressure dropped to 12 mm. Hg. Injection of adrenalin as the pressure fell was without effect. This was due in all probability to the fact that the drug did not reach the heart



because of the weak pulse and the low pressure. After vigorous massage the heart rate increased though the pressure tended to remain low. Anaesthesia was discontinued here and never used through the remainder of the experiment. The heart rate at this time was 120, the systolic pressure 40 and the diastolic pressure 30 mm. Hg.

One cc. of 1-10,000 adrenalin was injected. The pressure rose and very slight inhibition was effected. The pressure gradually fell and the heart became weaker and finally the heart practically stopped. Cardiac massage again effected a strengthened and increased beat, but small doses of adrenalin regularly produced the same results. Section of the vagi was without avail indicating that the action was peripheral.

This experiment shows the effect of small doses of chloroform when injected intravenously. Fibrillation did not occur but post-mortem examination of the heart showed that the organ was greatly distended.

#### DISCUSSION.

I have found that chloroform inhaled or injected intravenously produces a toxic effect on the heart resulting in dilatation and permanent weakness. This action is a direct one on the heart muscle since it occurs after section of the vagi and after atropine. The heart is slowed because of the toxic condition.

In a few experiments in which I have injected small amounts - 1-2 minims - of chloroform intravenously, I have found that the blood pressure after a very short and slight rise immediately begins to fall and the heart to weaken. If adrenalin is injected at this point paralytic dilatation and occasionally fibrillation are induced. In one experiment atropine produced the





same results. In all cases post-mortem examination of the heart showed a dilated organ. However, fibrillation was not effected in all cases. Resuscitation cannot be effected when once the heart has become paralytically dilated and ventricular fibrillation has supervened. However, if fibrillation has not occurred cardiac massage may effect automatic beating again.

Levy (56-57-58) is the only investigator that I have been able to find who has determined any definite relation between adrenalin and chloroform states that ventricular fibrillation is produced by cardiac stimulation under light chloroform anaesthesia, and that small intravenous injections of adrenalin under high percentages of chloroform vapor produce a condition of irritability in the ventricle similar to that observed to result under low percentages of chloroform alone. He also states that low tensions of chloroform administered to cats together with adrenalin produces fibrillation. He attributes death under chloroform anaesthesia to the low chloroform vapor which occurs at the beginning and at the end of administration and which produces an "irritable heart". Sensory stimulation either reflexly from the struggling or from the action of the vapor on the respiratory passages produces fibrillation.

In view of this fact Hare (41) states that chloroform as an anaesthetic is contraindicated after adrenalin has been used hypodermically or locally, and that if chloroform is used in such cases it should be preceded by atropin to nullify the action of the adrenalin.

Elliott (32) noted that dogs under ether despite the section of the vagus died suddenly due to heart failure with sudden



injection of adrenalin. He found large clots in the innominate vein and the right heart and hence attributed death to the intravenous clotting. Death did not occur when defibrinated dogs were used.

Oliver and Schafer encountered this trouble only in one of their experiments, but gave no explanation of it. Permanent inhibition of the heart under chloroform anaesthesia and following injection of adrenalin, I think is due primarily to weakening and dilatation of the organ induced by chloroform. While stoppage occurs more quickly and easily under light anaesthesia or low tension vapor than under deep anaesthesia or high tension vapour I have found complete inhibition to result under the latter condition. Adrenalin to a small degree causes distention of the heart.

Adrenalin by increasing the peripheral pressure causes an extremely high aortic pressure against which the heart cannot empty itself. Adrenalin at the same time by stimulating the sympathetic and the heart muscle directly tends to augment and accelerate the heart beat, but in consequence of the high aortic pressure and the toxic effect of the chloroform on the heart which causes it to dilate, the muscle fibers losing their normal elasticity, this action of adrenalin throws an added load on the already weakened heart inducing paralytic dilatation and sometimes fibrillation.

By injecting aconite I was able to produce ventricular fibrillation, however not until dilatation had occurred. In consequence of my findings I believe that paralytic dilatation occurs first and that ventricular fibrillation which may supervene on this condition is due to active centers in the heart muscle attempting





to re-establish a sequence of beats.

I do not believe this to be a compensatory dilatation of the heart - the heart dilating so that at each beat a greater amount of blood is forced into the system. I am of the opinion that this dilatation is toxic or paralytic in character and due in a large measure to the direct action of the chloroform on the heart muscle. It does not occur when the pressure is lowered by other means. It is proportional to the length of time and the amount of chloroform administered. It is terminal in character.

Although Gottlieb (40) working with dogs found that adrenalin injected intravenously would resuscitate a heart stopped by chloral hydrate and on this basis suggested that it might be used in chloroform narcosis with threatened heart collapse, I think that adrenalin is contraindicated wherever chloroform is used and that chloroform is contraindicated wherever adrenalin is employed.

That the blood pressure alone bears no relation either direct or reflex to the degree of inhibition I think is amply proven by my experiments. The pressure was raised artificially to a height equal to that produced by 1 cc. of 1-10,000 adrenalin without any evidence of inhibition. That the size of the dose is in part responsible for the degree of slowing is shown in experiment I. In this case 1 cc. of 1-100,000 produced a rise in pressure equal to that produced by 1 cc. of 1-10,000 but only the latter effected inhibition. That the increased blood pressure does not stimulate the inhibitory center and hence produce these results is proven by the fact that they occur after section of the vagi.

I have repeatedly found the inhibition to occur after the





pressure had returned to normal. In some experiments the pressure was increased to 300 mm. Hg. without any slowing being evident. I think the high aortic pressure is of paramount importance in producing these results.

# CONCLUSIONS.

1. Chloroform is toxic for heart muscle, effecting dilatation and weakening.
2. Inhibition under chloroform anaesthesia after adrenalin is due primarily to toxic or paralytic dilatation of the heart ventricular fibrillation at times supervening on this condition.
3. Adrenalin is contraindicated wherever chloroform is employed and chloroform wherever adrenalin is used.
4. The blood pressure has no definite reflex relation to the production of the condition, but has a most important direct action.
5. The adrenalin action is peripheral since it occurs after section of the vagi.
6. Increased pressure alone is not sufficient to produce the change.
7. Adrenalin increases the irritability of the vagus endings, and this irritability is further increased by chloroform.



TABLE 8.

Pulse	Pressure		Remarks
	Systolic	Diastolic	
180	120	114	Normal
172	142	136	After 1 cc. 1-100,000 adrenalin.
180	140	130	After 1 cc, 1-10,000 adrenalin.
Inhib.	18	--	10 seconds afterward.
164	140	126	After 1 cc. 1-100000 adrenalin.
114	120		Stimulation of right vagus.
			Chloroform used for anaesthesia,
160	120	102	After 1cc. 1-100,000 adrenalin.
47	120	116	After 1 cc. 1-10,000 adrenalin.
156-			Before stimulation of right vagus.
60			After stimulation of right vagus.
			Vagi cut.
136	104	98	Before 1 cc. 1-10,000 adrenalin.
62	80	74	After 1 cc. 1-10,000 adrenalin.





TABLE 9

Pulse	Pressure		Remarks.
	Systolic	Diastolic	
110	126	112	Normal.
210	230	196	After 1 cc. 1-10,000 adrenalin.
126	116	110	Before 2 cc. 1-10,000 adrenalin.
162	240	200	After 2 cc. 1-10,000 adrenalin.
			Chloroform substituted for ether anaesthesia.
100	138	130	Before 1-10,000 adrenalin.
120	208	190	After 1 cc. 1-10,000 adrenalin.
			Heart dilated and fibrillating.



TABLE 10.

Pulse	Pressure		Remarks.
	Systolic	Diastolic	
150	94	86	Normal
Imperceptible	12	--	After one minum of chloroform.
120	40	30	After massage.
90	74	56	After 1 cc. 1-10,000 adrenalin.
Imperceptible	18	16	100 seconds later.



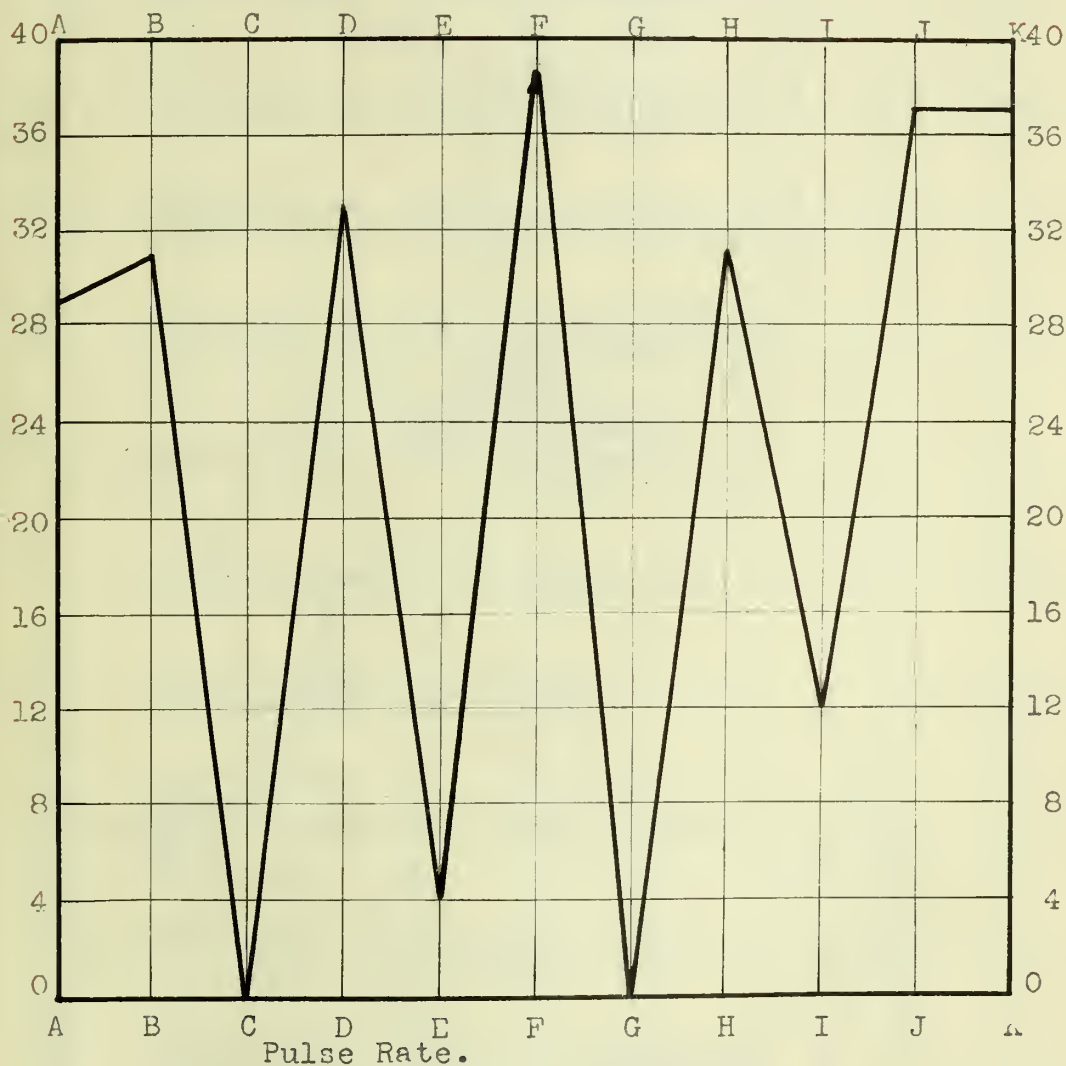
VII  
GRAPHS.





Graph 1

Showing the effect of adrenalin, when perfused through the brain, on the turtle heart.



A. Normal.

F. After salt perfusion.

B. After salt perfusion.

G. After adrenalin.

C. After adrenalin.

H. After salt perfusion.

D. After salt perfusion.

I. After dilute adrenalin.

E. After strychnine.

J. After salt perfusion.

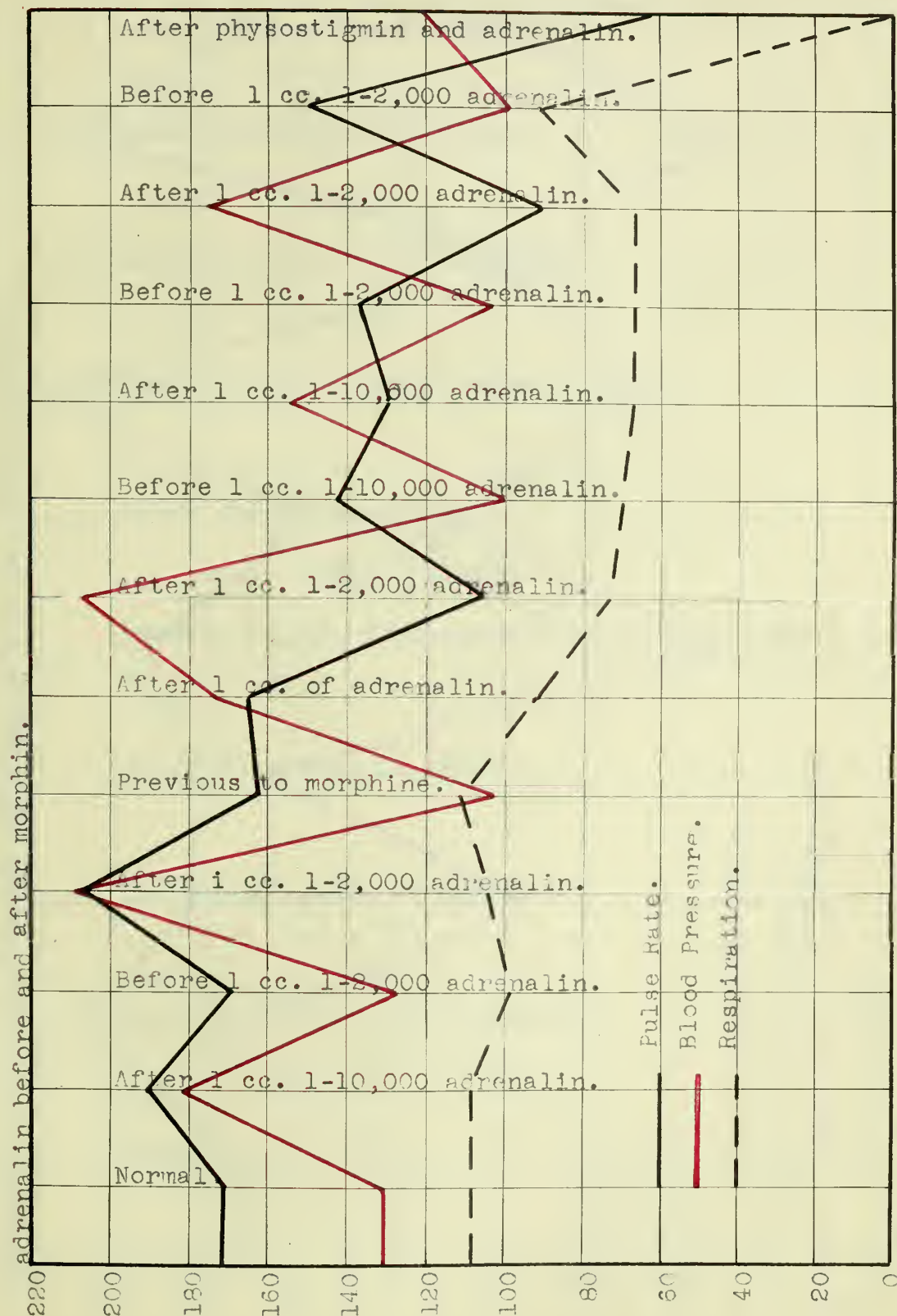


The following table shows the variation of the variable over time. The data is presented in two columns: Time and Value. The values are in units of 100.

Time	Value
1	100
2	200
3	100
4	300
5	100
6	400
7	100
8	500
9	100
10	600
11	100
12	700
13	100
14	800
15	100
16	900
17	100
18	1000
19	100
20	1100
21	100
22	1200
23	100
24	1300
25	100
26	1400
27	100
28	1500
29	100
30	1600
31	100
32	1700
33	100
34	1800
35	100
36	1900
37	100
38	2000
39	100
40	2100
41	100
42	2200
43	100
44	2300
45	100
46	2400
47	100
48	2500
49	100
50	2600

GRAPH 2.

Showing the relation of the heart rate and the blood pressure as influenced by







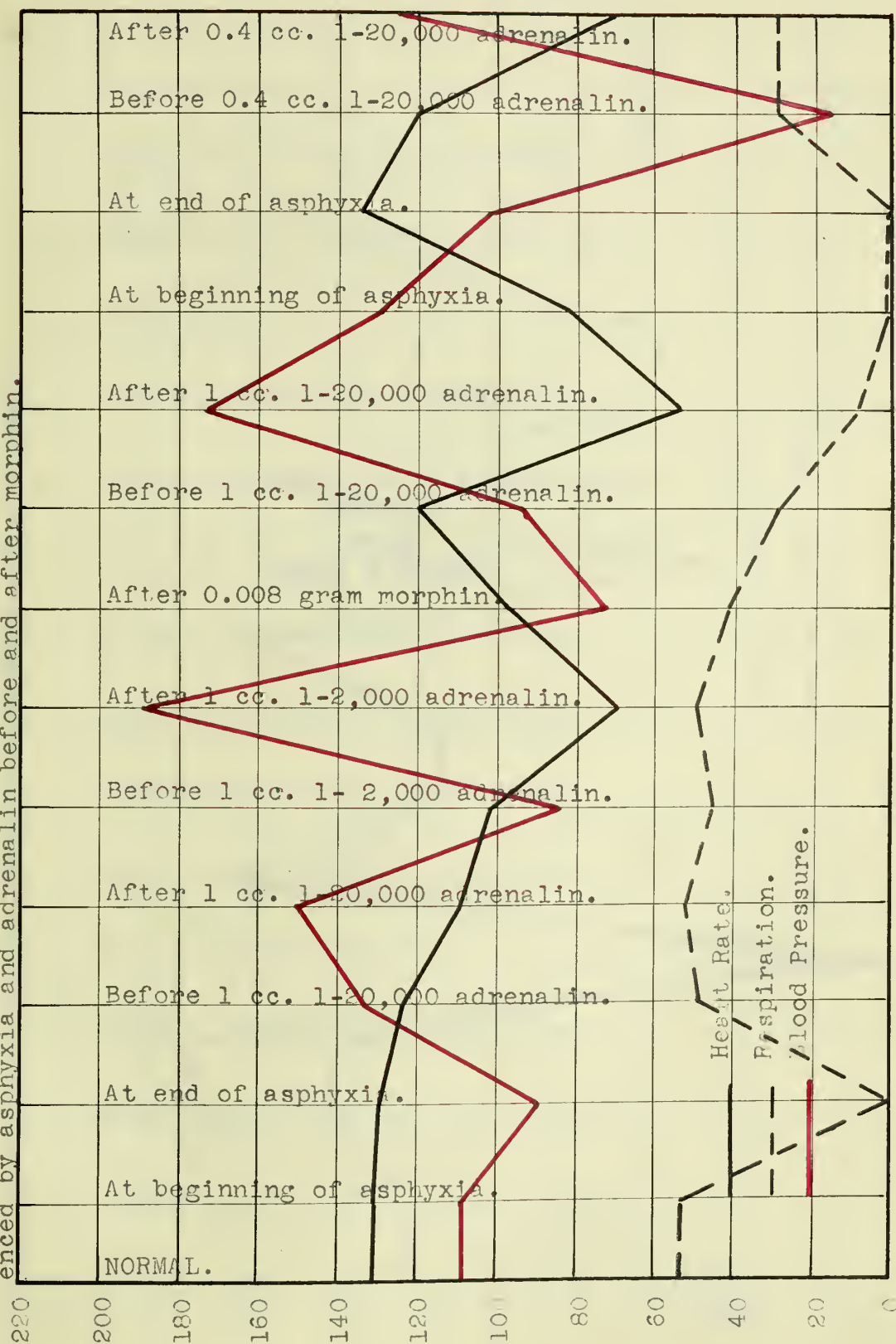




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GRAPH 4.

Showing the relation of the pulse, blood pressure and respiration as influenced by asphyxia and adrenalin before and after morphin.

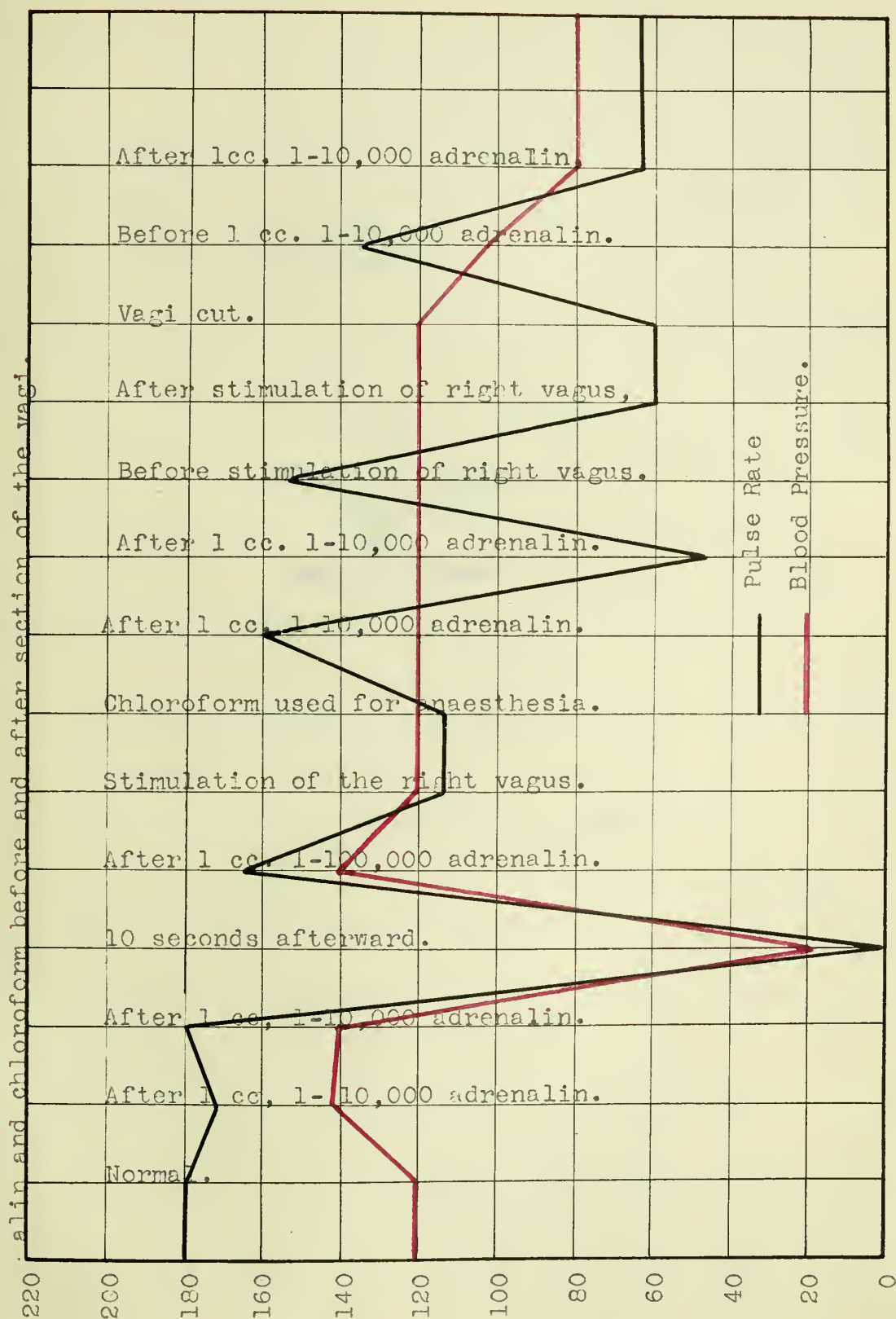


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GRAPH 5.

Showing the relation of pulse and blood pressure as influenced by adrenalin and chloroform before and after section of the vagi.





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